Original article

Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial

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Background: Some patients with severe asthma remain symptomatic and obstructed despite maximal recommended treatment. Tiotropium, a long-acting inhaled anticholinergic agent, might be an effective bronchodilator in such patients.
Objective: We sought to compare the efficacy and safety of 2 doses of tiotropium (5 and 10 μg daily) administered through the Respimat inhaler with placebo as add-on therapy in patients with uncontrolled severe asthma (Asthma Control Questionnaire score, ≥1.5; postbronchodilator FEV_1, ≤80% of predicted value) despite maintenance treatment with at least a high-dose inhaled corticosteroid plus a long-acting β_2-agonist.
Methods: This was a randomized, double-blind, crossover study with three 8–week treatment periods. The primary end point was peak FEV_1 at the end of each treatment period.
Results: Of 107 randomized patients (54% female patients; mean, 55 years of age; postbronchodilator FEV_1, 65% of predicted value), 100 completed all periods. Peak FEV_1 was significantly higher with 5 μg (difference, 139 mL; 95% CI, 96-181 mL) and 10 μg (difference, 170 mL; 95% CI, 128–213 mL) of tiotropium than with placebo (both $P < .0001$). There was no significant difference between the active doses. Trough FEV_1 at the end of the dosing interval was higher with tiotropium (5 μg: 86 mL [95% CI, 41-132 mL]; 10 μg: 113 mL [95% CI, 67-159 mL]; both $P < .0004$). Daily home peak expiratory flow measurements were higher with both tiotropium doses. There were no significant differences in asthma-related health status or symptoms. Adverse events were balanced across groups except for dry mouth, which was more common on 10 μg of tiotropium.
Conclusion: The addition of once-daily tiotropium to asthma treatment, including a high-dose inhaled corticosteroid plus a long-acting β_2-agonist, significantly improves lung function over 24 hours in patients with inadequately controlled, severe, persistent asthma. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: *Asthma, severe uncontrolled asthma, randomized controlled trial, anticholinergics, tiotropium*

Although the goal of asthma management is to achieve and maintain control of asthma symptoms, prospective studies have confirmed that a significant proportion of patients do not achieve this target, even after upward titration of an inhaled corticosteroid (ICS) plus a long-acting β_2-agonist (LABA).[1,2] The last recommended step in the Global Initiative for Asthma (GINA) guidelines is the addition of another treatment, such as antileukotrienes, theophyllines, anti-IgE, and immunosuppressants (eg, systemic corticosteroids or cyclosporine). Nevertheless, many patients remain both symptomatic and obstructed.[2] A potential alternative approach is the addition of a second bronchodilator with an alternative mode of action, the anticholinergic tiotropium bromide, which has been shown to be effective in patients with chronic obstructive pulmonary disease (COPD), in whom it is widely used.[3,4]

Tiotropium has a long duration of action, which is attributed to its slow dissociation from muscarinic receptors.[5] Also, because of their slower mode of action and generally smaller effect than short-acting β_2-agonists, there has been little use of anticholinergics in patients with asthma.[6] Nevertheless, the short-acting anticholinergic ipratropium has been shown in patients with stable asthma to produce statistically significant but rather modest improvements in symptoms and morning peak expiratory flow (PEF).[7] In patients with acute asthma, the addition of ipratropium to a β_2-agonist resulted in significant improvement in PEF and reduced the risk of hospital admissions.[8] The GINA guidelines state that the long-term benefits of anticholinergics (ipratropium) have not been established and point to their potential as an alternative bronchodilator for patients who experience adverse effects, such as tachycardia, arrhythmia, and tremor, from the use of rapid-acting β_2-agonists.[2] The use of long-acting anticholinergics is not commented on in the GINA guidelines.

Beneficial effects of tiotropium maintenance dosing in patients with asthma have been reported in cohort studies and case reports.[9-12] More importantly, Peters et al[13] recently demonstrated in patients with mild-to-moderate asthma uncontrolled with only low-dose ICSs that the addition of tiotropium yielded superior improvements in morning and evening PEF, prebronchodilator FEV_1, symptoms, and asthma control days compared with doubling the dose of ICSs. In the same study the use of tiotropium was found not to be inferior to salmeterol. Bateman et al,[14] in a

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Abbreviations used
AUC: Area under the curve
COPD: Chronic obstructive pulmonary disease
FVC: Forced vital capacity
GINA: Global Initiative for Asthma
ICS: Inhaled corticosteroid
LABA: Long-acting β_2-agonist
Mini-AQLQ: Mini–Asthma Quality of Life Questionnaire
PEF: Peak expiratory flow

companion study in this issue, report that tiotropium was more effective than placebo and noninferior to salmeterol in maintaining improved lung function in patients with moderate persistent asthma with the B16–Arg/Arg genotype receiving regular ICSs.

Tiotropium has not been evaluated in a randomized controlled trial in patients with severe uncontrolled asthma. The aim of the study presented here was to evaluate the efficacy and safety of added tiotropium in asthmatic patients whose symptoms are inadequately controlled with at least high-dose ICS plus LABA treatment (GINA step 4-5).[2]

METHODS

Trial design

This randomized, double-blind, placebo-controlled, crossover study with three 8–week treatment periods was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent for participation in the clinical trial. The trial was registered at www.clinicaltrials.gov (NCT00365560). After a 2-week run-in period, eligible patients were randomized and entered a 24–week, double-blind treatment period. Visits occurred at the start of the trial (screening), at randomization (baseline), and at the end of each treatment period. There was no washout period between treatments. This article's Online Repository at www.jacionline.org contains details on design, inclusion criteria, and methods.

Participants

Patients were outpatients aged 18 to 75 years with at least a 5-year history of asthma and a current diagnosis of severe persistent asthma (for assessment, see this article's Online repository). They were persistently obstructed and symptomatic (Asthma Control Questionnaire[15] score, ≥1.5; postbronchodilator FEV_1 of ≤80% of predicted value[16] and ≤70% of forced vital capacity [FVC] 30 minutes after inhalation of 4 × 100 μg of salbutamol at screening) despite therapy with a high-dose ICS (≥800 μg of budesonide or equivalent, see this article's Online Repository) and a LABA. Sustained-release theophylline, leukotriene modifiers, and oral glucocorticosteroids were also permitted in stable doses. Patients had to have never smoked or not have smoked for a year and have a smoking history of less than 10 pack-years. The main exclusion criteria were COPD, serious concomitant illnesses, and certain concomitant medications (see this article's Online Repository).

Trial medication

All patients received each of 3 treatments in a random sequence for 8 weeks in a crossover design (5 or 10 μg of tiotropium or matching placebo administered as 2 actuations once daily through the Respimat inhaler). Study medication was taken in the morning as add-on therapy to each patient's maintenance asthma therapy. A salbutamol metered-dose inhaler (100 μg per puff) was provided as rescue medication throughout the trial.

Study end points

Throughout the 24-week treatment period, patients recorded PEF and FEV_1 values (recorded from the same maneuver) twice daily at home by using the Asthma Monitor AM2+ and answered the daily questions in the electronic diary component of this device. The primary end point was the peak FEV_1 (within 3 hours after dosing) determined at the end of each 8–week treatment period by means of supervised spirometry in the clinic. Baseline was the pretreatment FEV_1 measured in the morning 10 minutes before administration of any medication. This was followed by maintenance medication, which was followed in turn by any study medication. FEV_1 was determined over a 24–hour period in a subset of patients who were participants in centers where this was feasible. Secondary end points included trough FEV_1 and peak and trough FVC at the end of each 8–week treatment period, the area under the curve (AUC) of the first 3 hours of FEV_1 (FEV_1 $AUC_{0\text{-}3h}$) and FVC (FVC $AUC_{0\text{-}3h}$) and weekly means of predose morning and evening PEF and FEV_1, asthma symptoms (5-point rating scale), use of rescue medication in the last 5 weeks of treatment, asthma symptom-free days, and quality of life as assessed by the Mini-Asthma Quality of Life Questionnaire (Mini-AQLQ). Analysis of the weekly mean PEF was prespecified to exclude the first 3 weeks so as to avoid a possible carryover effect in a crossover design without a washout period. Safety end points included all adverse events, pulse rate, and blood pressure for the first 3 hours after dosing and routine blood chemistry and hematologic studies. For further details, see this article's Online Repository.

Randomization and masking

After the run-in period, patients were randomly assigned (1:1:1 ratio) to one of 3 treatment sequences. Randomization was in blocks of 6 per center, with no other stratification. The randomization schedule was generated by using a pseudorandom number generator and a supplied seed number. The randomization schedule was generated by using a validated system (PMX CTM Release 3.3.0 HP2; Propack Data GmbH, Karlsruhe, Germany).

Statistical analysis

All statistical analyses were prespecified, with the exception of the subgroup analyses, where only analysis by sex was prespecified. Testing followed a hierarchical sequence: superiority of 10 μg of tiotropium versus placebo, superiority of 5 μg of tiotropium versus placebo, and noninferiority of 5 μg of tiotropium versus 10 μg of tiotropium for the primary end point (noninferiority Δ, 50 mL). Each step was considered confirmatory only if all previous steps were successful. The ordered 1-sided hypotheses were tested based on adjusted means of peak FEV_1 response at the end of the 8–week treatment period from an analysis of covariance with terms for baseline FEV_1 (pretreatment on randomization day), pooled center, patient within pooled center, period, and treatment. With 84 completed patients, the study had 95% power to detect a difference of 100 mL in peak FEV_1 ($\alpha = .025$, 1-sided) by using a 2-group *t* test, assuming an SD of 250 mL for within-patient differences. All analyses were based on the intention-to-treat principle. Statistical comparisons of secondary end points (also analysis of covariance) were exploratory, with a noninferiority Δ for FVC of 80 mL. Statistical analysis was performed with SAS (SAS Institute, Inc, Cary, NC). Details of the methods and statistical analysis are provided in this article's Online Repository.

RESULTS

Patients were enrolled between August 2006 and November 2007. Of 132 patients screened, 110 were eligible for the trial, 107 were randomized, and 100 completed all 3 treatment periods (Fig 1). The demographic characteristics of randomized patients at screening are summarized in Table I. Medication used before the screening visit comprised LABAs and ICSs (per inclusion criteria), rapidly acting β-agonists (77%), short-acting anticholinergics (21%; no long-acting anticholinergics were used), antihistamines (22%), theophyllines (13%), and antileukotrienes (13%). Two patients used a maintenance dose of oral corticosteroids.

Differences between treatment responses are summarized in Table II (mean responses are shown in Table WA1 in this article's Online Repository at www.jacionline.org). The adjusted mean

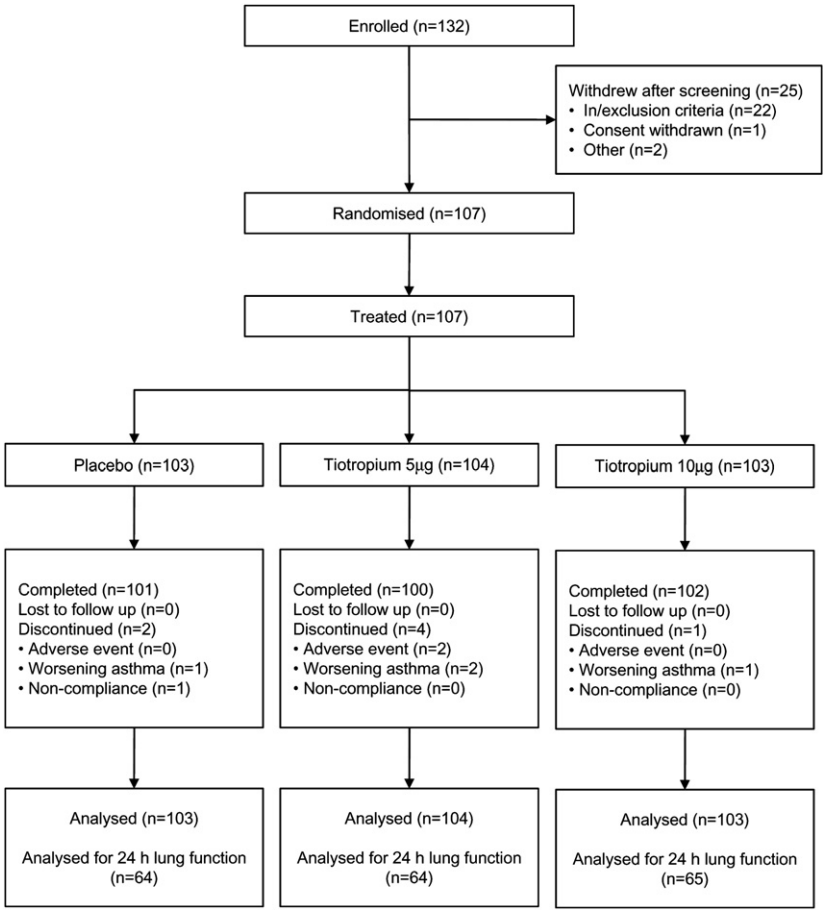

FIG 1. Screening, randomization, and study completion.

peak FEV_1 response in the first 3 hours after dosing at the end of the 8–week treatment period (the primary end point) was significantly superior to placebo with both tiotropium doses (5-μg difference from placebo, 139 mL [95% CI, 96-181 mL], $P < .001$; 10-μg difference from placebo, 170 mL [95% CI, 128-213 mL], $P < .001$; Fig 2). Between the tiotropium dose groups, no statistical difference could be shown (difference between doses, 32 mL [95% CI, 11-75 mL]; $P = 0.40$, noninferiority). There were no period effects or treatment-period interactions. Consistent responses with the primary end point were apparent for all secondary end points: trough FEV_1 (end of dosing interval) was significantly greater with both tiotropium doses compared with placebo (5-μg difference from placebo, 86 mL [95% CI, 41-132 mL], $P < .001$; 10-μg difference from placebo, 113 mL [95% CI, 41-132 mL], $P < .001$), but no significant difference between the tiotropium dose groups could be shown ($P = .31$, noninferiority).

The 24-hour spirometric assessments in a subgroup of patients (n = 67) also showed significant improvements in FEV_1 for both active treatments compared with placebo (Fig 3). FEV_1 $AUC_{0\text{-}24h}$ was significantly greater with both doses compared with placebo (5-μg difference from placebo, 86 mL [95% CI, 41-132 mL], $P = .0012$; 10-μg difference from placebo, 90 mL [95% CI, 38-142 mL], $P < .001$). There was no statistical difference between the active treatments.

Both doses of tiotropium were significantly superior compared with placebo in all other spirometric assessments (ie, mean peak FVC in the first 3 hours after dosing, trough FVC, and FVC $AUC_{0\text{-}3h}$), as well as in the subgroup of patients with 24-hour spirometric assessments (n = 67) for FVC $AUC_{0\text{-}24h}$ (Table II and Figs 2 and 3). Based on FVC end points, the 5-μg dose was not inferior to 10 μg of tiotropium.

The weekly mean predose morning and evening PEFs were greater for both tiotropium doses compared with placebo (Table II and Fig 4). Mean morning PEF with 10 μg of tiotropium was superior to 5 μg of tiotropium (difference, 7.4 L/min [95% CI, 0.7-14.1 L/min], $P = .030$). The differences in evening PEF followed the same pattern: superiority of both doses compared with placebo and a significant difference between the 2 doses (Table II).

There were only small and nonsignificant differences in the use of rescue medication among the 3 periods. The mini-AQLQ and the electronic asthma diary showed a minimal change in mini–AQLQ scores over the entire treatment period of 0.1 points for both active treatments compared with placebo (not significant) and no significant differences in the symptom scores measured with the electronic diary (see Tables WA2-4 in this article's Online Repository at www.jacionline.org).

The treatment effects of both doses of tiotropium compared with placebo were not significantly altered in subgroup analyses based on sex, FEV_1 percent predicted or reversibility at screening, smoking status, or asthma duration. Nevertheless, the improvements with both 5 and 10 μg of tiotropium versus placebo were numerically larger in the patients with a lower FEV_1, in ex-smokers than in patients who had never smoked, and in patients

TABLE I. Baseline characteristics of the randomized patients at screening

Total no. of patients	107
Female subjects, no. (%)	58 (54.2)
Age (y)	54.8 (11.7)
Smoking status	
Never smoked, no. (%)	73 (68.2)
Exsmoker, no. (%)	34 (31.8)
Smoking history, mean pack-years (range)	5.6 (0-9.0)
Age of onset of asthma (y)	25.2 (18.5)
Duration of asthma (y)	29.7 (16.8)
Mini-AQLQ	4.8 (1.1)
ICS + LABA as per protocol % of patients	100
ICS dose (μg)	1235 (749)
Rapidly-acting β_2-agonists (% of patients)	77
Mean daily number of puffs	3.9 (3.6)
Short-acting anticholinergics (% of patients)*	21
Theophyllines (% of patients)	13
Antileukotrienes (% of patients)	13
Antihistamines (% of patients)	22
FEV_1 (% predicted)	
Prebronchodilator	58.0 (11.6)
By category of % predicted, no. (%)	
<35%	5 (4.7)
35% to 50%	20 (18.7)
50% to 60%	29 (27.1)
>60%	53 (49.5)
Postbronchodilator	65.3 (11.4)
Reversibility (mL), mean	218 (0.22)
Percentage of baseline	14.0 (14.4)
FEV_1/FVC (%)	
Prebronchodilator	56.1 (9.5)
Postbronchodilator	57.9 (8.7)
PEF (% predicted)	72.2 (18)

Data are presented as means (SDs) unless specified otherwise.
*Stopped during the study.

TABLE II. Analysis of efficacy at week 8

Comparison	Difference	95% CI	*P* value
Peak FEV_1 response (mL; primary end point)			
5 μg Tiotropium–placebo	139	96 to 181	<.001
10 μg Tiotropium–placebo	170	128 to 213	<.001
10 μg Tiotropium–5 μg tiotropium	32	−11 to 75	.40*
Trough FEV_1 response (mL)			
5 μg Tiotropium–placebo	86	41 to 132	<.001
10 μg Tiotropium–placebo	113	67 to 159	<.002
10 μg Tiotropium–5 μg tiotropium	26	−20 to 72	.31*
$AUC_{0\text{-}3h}$ FEV_1 response (mL)			
5 μg Tiotropium–Placebo	126	87 to 165	<.001
10 μg Tiotropium–placebo	148	109 to 188	<.0011
10 μg Tiotropium–5 μg tiotropium	22	−17 to 62	.17*
FVC peak response (mL)			
5 μg Tiotropium–placebo	121	67 to 175	<.001
10 μg Tiotropium–placebo	107	53 to 162	<.001
10 μg Tiotropium–5 μg tiotropium	−14	−68 to 41	<.001*
Trough FVC response (mL)			
5 μg Tiotropium–placebo	127	67 to 187	<.001
10 μg Tiotropium–placebo	119	60 to 179	<.001
10 μg Tiotropium–5 μg tiotropium	−7	−67 to 52	.004*
$AUC_{0\text{-}3h}$ FVC response (mL)			
5 μg Tiotropium–placebo	116	69 to 163	<.001
10 μg Tiotropium–placebo	97	51 to 144	<.001
10 μg Tiotropium–5 μg tiotropium	−19	−65 to 28	<.001*
$AUC_{0\text{-}24h}$ FEV_1 [mL]†			
5 μg Tiotropium–placebo	86	35 to 138	.001
10 μg Tiotropium–placebo	90	38 to 142	.001
10 μg Tiotropium–5 μg tiotropium	4	−48 to 55	.08*
Morning PEF (L/min), average for weeks 4-8			
5 μg Tiotropium–placebo	7.9	1.2 to 14.7	.02
10 μg Tiotropium–placebo	15.3	8.6 to 22.0	<.001
10 μg Tiotropium–5 μg tiotropium	7.4	0.7 to 14.1	.03
Evening PEF (L/min), average for weeks 4-8			
5 μg Tiotropium–placebo	14.7	6.8 to 22.5	<.001
10 μg Tiotropium–placebo	23.3	15.4 to 31.1	<.001
10 μg Tiotropium–5 μg tiotropium	8.6	0.8 to 16.5	.03

Lung function was measured as the change from baseline (visit 2) values before any maintenance or study medication. At the on-treatment visits, this was immediately followed by the usual medication (including ICS plus LABA), which in turn was followed by the study medication. Full analysis set (signifying intention-to-treat): placebo (n = 103), 5 μg of tiotropium (n = 104), and 10 μg of tiotropium (n = 103). Values are presented as adjusted means, 95% CIs, and *P* values (superiority) of treatment differences unless otherwise stated.
*Noninferiority *P* values.
†Subgroup full analysis set: placebo (n = 64), 5 μg of tiotropium (n = 64), and 10 μg of tiotropium (n = 65).

with a larger response to β_2-agonists (see Table WA5 Online repository in this article's Online Repository at www.jacionline.org).

Adverse events were reported in 40%, 42%, and 50% of patients receiving placebo, 5 μg of tiotropium, and 10 μg of tiotropium, respectively. Among the events reported by at least 2% of patients, only dry mouth, cough, headache, and productive cough occurred at a higher incidence during active treatment compared with placebo treatment (Table III). In 7 patients events were assessed to be drug related: asthma exacerbation (placebo), upper abdominal pain (5 μg of tiotropium), gastrointestinal reflux disease, oral candidiasis, and dry mouth in 4 patients (10 μg of tiotropium). Serious adverse events were reported for 5 patients: 2 while receiving placebo (osteoarthritis and an asthma exacerbation), 2 while receiving 5 μg of tiotropium (pneumonia/pleurisy, treatment discontinued, and gastritis), and 1 while receiving 10 μg of tiotropium (angioedema). All were labeled as serious because of hospitalization, none were life-threatening, and none were considered drug related. No blood pressure, pulse rate, laboratory test, or electrocardiographic abnormalities were observed that could be attributed to the add-on study drug or dose.

DISCUSSION

Tiotropium resulted in significant bronchodilatation in patients with severe asthma not adequately controlled by maximal treatment according to guidelines, including a combination of high-dose ICS plus LABA treatment. The bronchodilator effect was not different between the 2 doses and was not associated with significant improvement in any related outcome.

Although most patients with asthma can achieve control with appropriate medication according to the guidelines, some patients remain symptomatic despite maximal therapy containing at least

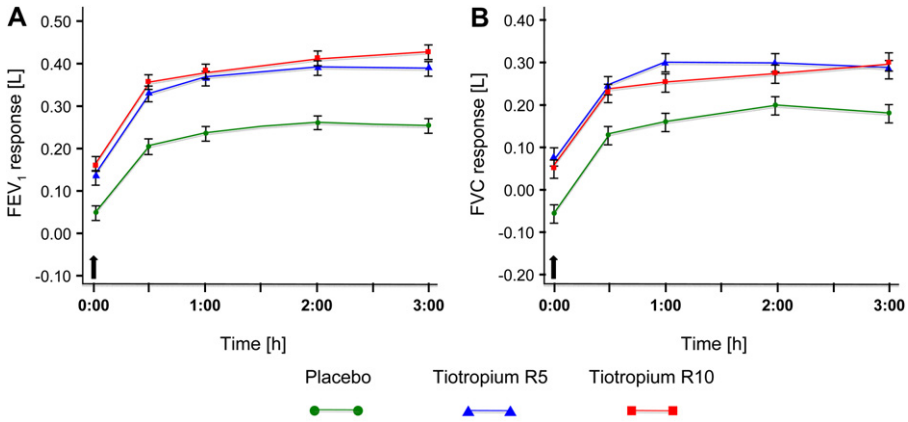

FIG 2. FEV_1 **(A)** and FVC **(B)** responses relative to baseline values within 3 hours after dosing after 8 weeks of treatment. The difference in level at *0:00 h* is the trough effect of tiotropium administered 24 hours earlier. The measurement obtained at baseline (visit 2 before any maintenance or study medication) is defined as the baseline value. At the on-treatment visits, this was immediately followed by the usual medication (including ICS plus LABA), and this in turn was followed by the study medication. *Error bars* represent SEMs. *Arrows* indicate the timing of the maintenance medication: ICS plus LABA. *Tiotropium R5*, 5 μg of tiotropium; *Tiotropium R10*, 10 μg of tiotropium.

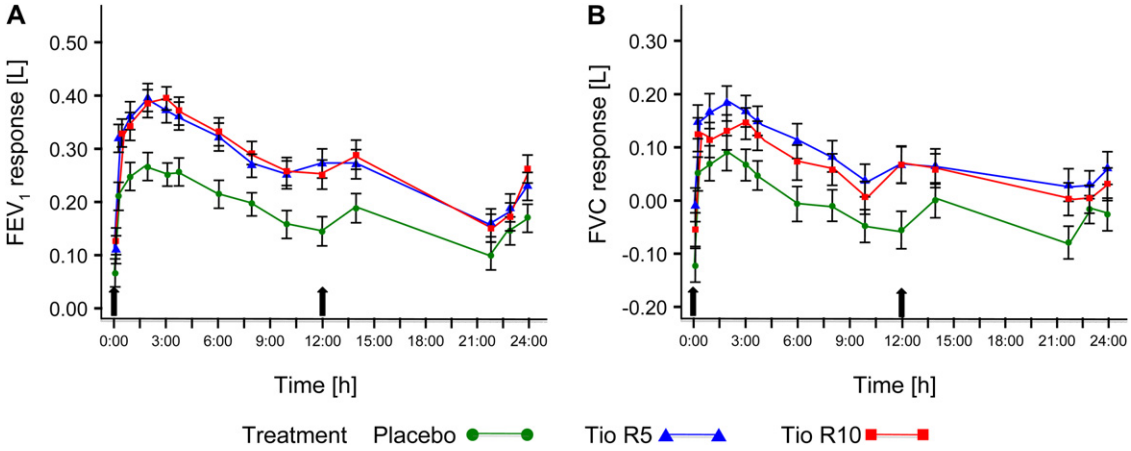

FIG 3. Twenty-four-hour FEV_1 **(A)** and FVC **(B)** responses as shown in Fig 2 in the subgroup of patients with 24-hour assessments (n = 67). The baseline value was defined on visit 2 before any maintenance or study medication. At the on-treatment visits, this was immediately followed by the usual medication (including ICS plus LABA), which was followed in turn by the study medication. The afternoon dosing of ICS plus LABA treatment was also taken. *Error bars* represent SEMs. *Arrows* indicate the timing of the maintenance medication: ICS plus LABA. *Tio R5*, 5 μg of tiotropium; *Tio R10*, 10 μg of tiotropium.

high-dose ICS plus LABA treatment (GINA steps 4 and 5), and many of these patients also have persistent airways obstruction.[1,2] This study was designed for this group of patients with severe persistent asthma, multiple exacerbations, high health care resource use, and therefore high unmet medical needs.[17,18]

This study documents a clear superiority of tiotropium compared with placebo in asthmatic patients whose symptoms are not controlled with at least ICS plus LABA treatment in terms of primary and secondary spirometric end points at the end of 8 weeks of treatment. The improvement in peak FEV_1 of 139 to 170 mL with tiotropium was measured while patients were still receiving their maintenance treatment with high-dose ICS plus LABA treatment. The effect of the bronchodilatation caused by the LABAs that all patients received was not measured, but during reversibility testing at screening with the short-acting β_2-agonist salbutamol, 218 mL of bronchodilatation was measured. The 139 to 170 mL improvement with tiotropium can be seen as occurring in addition to such an effect of the long-acting β-adrenergic bronchodilator.

The FEV_1 improvements seen with tiotropium maintenance therapy in our study of patients with severe uncontrolled asthma receiving maintenance dosing with high-dose ICS plus LABA treatment (steps 4-5) are of similar magnitude to those seen in subjects with milder asthma uncontrolled with low-dose ICSs in a recent study by Peters at al[13] with the tiotropium Handihaler dry powder device. They are also comparable with those seen in patients with COPD with the Handihaler, where the effects have mostly been measured without concomitant LABA therapy.[19-21] The approved dose is 5 μg with the current Respimat inhaler in patients with COPD,[22] in whom the dose is equipotent to 18 μg through the Handihaler dry powder inhaler.[23]

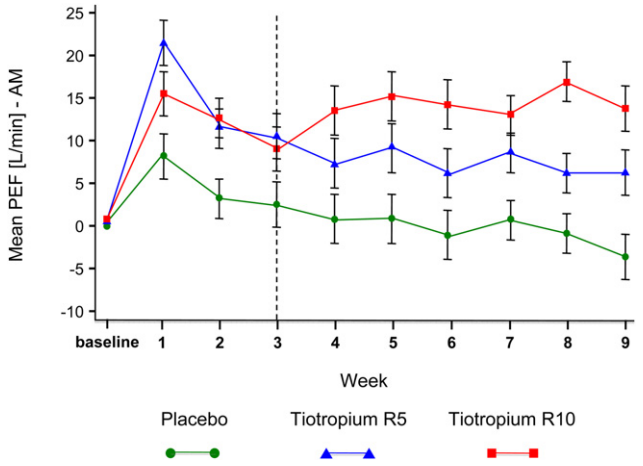

FIG 4. Mean weekly morning PEF measured before dosing in the last 5 weeks of the 8–week treatment period. Note: the first 3 weeks of the treatment period were prespecified as probably reflecting a carryover effect of the previous treatment because there was no washout period between treatments. *Error bars* represent SEMs.

TABLE III. Adverse events reported by at least 2% of randomized patients in any treatment group

	Placebo (n = 103)	5 μg Tiotropium (n = 104)	10 μg Tiotropium (n = 103)
Patients with any AE	41 (39.8)	44 (42.3)	51 (49.5)
Nasopharyngitis	11 (10.7)	9 (8.7)	10 (9.7)
Asthma deteriorations*	11 (10.7)	10 (9.6)	9 (8.7)
Cough	3 (2.9)	6 (5.8)	4 (3.9)
Dyspnea	5 (4.9)	5 (4.8)	1 (1.0)
Dry mouth	1 (1.0)	2 (1.9)	7 (6.8)
Headache	1 (1.0)	3 (2.9)	2 (1.9)
Diarrhea	4 (3.9)	2 (1.9)	1 (1.0)
Influenza	1 (1.0)	1 (1.0)	4 (3.9)
Sinusitis	2 (1.9)	3 (2.9)	2 (1.9)
Hypertension	3 (2.9)	2 (1.9)	1 (1.0)
Vomiting	4 (2.9)	2 (1.9)	2 (1.9)
Respiratory tract infection	2 (1.9)	1 (1.0)	2 (1.9)
Productive cough	0 —	2 (1.9)	2 (1.9)
Pneumonia	0 —	2 (1.9)	0 —
Dysphonia	1 (1.0)	1 (1.0)	1 (1.0)
Pharyngolaryngeal pain	0 —	0 —	1 (1.0)
Abdominal pain, upper	0 —	2 (1.9)	0 —
Back pain	0 —	0 —	1 —

Data are presented as numbers (percentages) of patients in descending order according to frequency in the 10 μg of tiotropium group.
*The official MedDRA term was asthma. This consisted mainly of exacerbations, routinely treated with prednisolone and occasionally with antibiotics only.

Subgroup analyses identified no characteristics that were significantly related to responder status, which perhaps is not surprising given the fact that only 107 patients were included. Nevertheless, the improvement in FEV_1 with tiotropium was slightly better in patients with lower FEV_1 and in patients with limited smoke exposure in the past (as opposed to no smoke exposure) that could be interpreted as COPD-like features.[24] However, the effect was also better in patients with greater β_2-agonist reversibility, which is more asthma like. All patients were carefully selected with a typical history of asthma and documented significant reversibility, PEF variability, or hyperresponsiveness and had a median age at onset of asthma of 25 years.

All secondary spirometric parameters showed improvements with tiotropium over placebo that were consistent with the primary end point, including trough FEV_1, FEV_1 $AUC_{0\text{-}3h}$, and peak and trough FVC and FVC $AUC_{0\text{-}3h}$. The bronchodilator effects of tiotropium were sustained for 24 hours, which is apparent from the trough FEV_1 measured 24 hours after dosing and immediately before the next dose. In a subgroup comprising more than half of the patients, the complete 24-hour time course of FEV_1 was assessed (Fig 3). All 3 treatments, including placebo, showed a steep increase after the morning dose, reflecting the administration of LABAs and a morning increase with circadian rhythm (all treatment groups) plus tiotropium's effects (active treatment groups only). The second peak in all curves 12 hours after the morning medications can be attributed to the evening LABA dose; the significant difference in FEV_1 response between the tiotropium groups and the placebo group is sustained.

The improvements in PEFs are in accordance with the data of Peters et al[13] and Bateman et al[14] in this issue in patients with moderate persistent asthma not controlled with ICSs. The bronchodilator effectiveness of 5 μg of tiotropium through a Respimat inhaler once daily was not inferior to that of the LABA salmeterol administered twice daily when added to maintenance treatment with ICSs.

The strength of our study is the power to find changes in the primary end point of FEV_1. Although all secondary lung function outcomes showed significant improvements, the size of the study limited the ability to find changes in secondary patient-reported outcomes. The crossover design without a washout period and the short study duration will have further limited the ability to find changes in patient-reported outcomes, such as asthma-related health status and use of rescue medication. The recently published study by Peters et al,[13] a study double the current size and with longer follow-up in subjects with mild-to-moderate asthma, describes significant improvements in symptoms and asthma control days but not in exacerbations or quality of life with tiotropium when compared with doubling the dose of ICS or when compared with salmeterol.[13] We suggest that the important outcome of reduction of exacerbations should now be studied in longer trials with sufficient numbers of patients.

The adverse event profile was balanced across the treatment groups, except for more reports of related adverse reactions in the gastrointestinal system organ class in the 10-μg tiotropium group, mostly complaints of dry mouth. These are known systemic anticholinergic effects listed as undesirable effects from the COPD database. These reactions were not a reason for discontinuation in any patient. Because increasing the dose of tiotropium from 5 to 10 μg when delivered through the Respimat inhaler offered no significant additional benefit in terms of FEV_1 bronchodilatation and only a small benefit in PEF, we suggest that the registered dose in patients with COPD, 5 μg of tiotropium administered through a Respimat inhaler once daily, is also an appropriate dose in most patients with severe asthma.

In animal models of allergic asthma, it has been shown that tiotropium has anti-inflammatory effects.[25,26] No changes in sputum eosinophilia or exhaled nitric oxide levels were found by Peters et al,[13] but the study was performed in subjects with moderately severe asthma and with almost no inflammation in these parameters at baseline. In our relatively short proof-of-concept study in patients with severe uncontrolled asthma

focusing on lung function, inflammatory parameters and exacerbation rates were not evaluated. Our positive results, in combination with those of Peters et al[13] and of the companion study reported by Bateman et al,[14] suggest the need for exploration of the potential of tiotropium in asthmatic patients not only in reducing the time to first exacerbation but also in improving inflammatory parameters, such as eosinophilia.

In summary, adding tiotropium once daily as maintenance treatment through the Respimat inhaler in addition to at least high-dose ICSs combined with LABAs offers significant potential to improve airway patency in patients with severe persistent asthma who are still symptomatic and obstructed on maximal therapy.

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Clinical implications: Adding tiotropium to maintenance therapy with high-dose ICS plus LABA treatment might result in marked bronchodilatation in patients with severe uncontrolled asthma who remain symptomatic and obstructed despite optimal therapy.

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